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Single-step synthesis of salans and substituted salans by Mannich condensation

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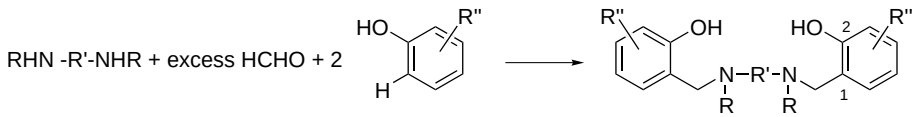
Abstract—A convenient route for the synthesis of a variety of salan-type compounds is introduced. The synthesis is based on a single-step Mannich condensation between readily available starting materials: primary or secondary amines, formaldehyde and substituted phenols. This methodology is suitable for the preparation of chiral salans as well, which may find applications in asymmetric catalysis. © 2001 Elsevier Science Ltd. All rights reserved.

The continuing search for new ligand systems for transition metals has drawn considerable interest to chelating amino and hydroxy compounds.[1] Compounds of the salen family have been studied extensively for many purposes and applied mostly in catalysis.[2–4] Salens are usually synthesized by condensing salicyl aldehydes and diamino compounds. Salan compounds (reduced salens)[5–9] have also been investigated for similar purposes. They are usually synthesized by reducing the corresponding salens to give the tetrahydrosalens, consisting of two secondary amine groups.[5–9] Previously, the preparation of *N*,*N*′-disubstituted salans required additional steps of substitution on the salans,[10–12] or alternatively, relied on reacting secondary amines with salicylaldehydes, followed by reduction.[13,14] We introduce herein, a *single-step* synthetic procedure enabling the preparation of a variety of salan compounds, as well as *N*,*N*′-disubstituted salans in high yields, which may serve as ligands for metal-based catalysts, from readily available highly versatile starting materials.[15] Based on this procedure, chiral compounds may be prepared as well.[12]

These *N*,*N*′-bis(2-hydroxyarylmethyl)-diamine compounds are synthesized by a Mannich condensation of substituted phenols, formaldehyde and diamines (Scheme 1). Thus, heating a solution of 10 mmol of *N*,*N*′-dimethylethylenediamine, 2 equiv. of 2,4-di-*tert*-butylphenol and an excess of 37% aqueous formaldehyde (10 equiv.) in 10 ml of methanol at reflux for 2 h, gave **1** (Scheme 1) in 88% yield as a colorless solid, that crystallized out of the reaction mixture, and was isolated by filtration. The other disubstituted salans



1: R = Me, R' = CH_2CH_2, R'' = 3,5-di-*tert*-butyl, 88% yield
2: R = Bn, R' = CH_2CH_2, R'' = 3,5-di-*tert*-butyl, 96% yield
3: R = Et, R' = CH_2CH_2, R'' = 3,5-di-*tert*-butyl, 71% yield
4: R = Me, R' = CH_2CH_2, R'' = 3,5-dimethyl, 82% yield
5: R = Me, R' = CH_2CH_2, R'' = 4,5-dimethyl, 88% yield
6: R = H, R' = CH_2CH_2, R'' = 3,5-di-*tert*-butyl, 90% yield
7: R = Me, R' = $CH_2CH_2CH_2$, R'' = 3,5-di-*tert*-butyl, 100% yield
8: R = H, R' = $CH_2CH_2CH_2$, R'' = 3,5-di-*tert*-butyl, 87% yield

Scheme 1.

Keywords: salans; substituted salans; Mannich condensation; chiral compounds.

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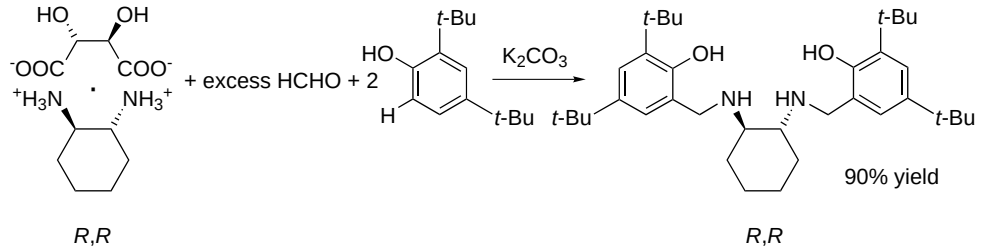

Scheme 2.

described in Scheme 1 were obtained cleanly by analogous reactions in 70–100% yields.† This methodology carries a further advantage; as the substituted salicylaldehydes employed in previous syntheses are replaced by substituted phenols and formaldehyde, the scope of possible salans is broadened since a large variety of substituted phenols are commercially available.

The bridging unit between the two nitrogen atoms, the substituents on the amine group, and the substitution pattern on the phenols may be varied, thus this simple methodology gives rise to a variety of salans (Scheme 1). The bulk of the aromatic ring substituents is expected to play a significant role in the reactivity of the resulting metal complexes by directing incoming substrates. Similar effects may arise from varying the nitrogen substituents. The length of the bridging unit between the nitrogen atoms may also be designed to fit binding to a particular metal, by proper choice of the diamine.

Interestingly, this methodology was found to be successful for primary amines as well (Scheme 1, entries 6, 8). Despite our concerns regarding the reaction selectivity, the desired unsubstituted salans formed, crystallized out of the reaction mixture, and were isolated by filtration in similar yields to those obtained for the substituted compounds. NMR analysis indicated no contamination by tertiary amines. These compounds may be potentially used directly as ligands, or serve as starting materials for hexadentate ligands,[16] upon further substitution on the secondary nitrogen atoms.

We attempted the synthesis of chiral compounds, which may be employed as ligands in chiral complexes for use in asymmetric catalysis.[17] *Rac-trans*-1,2-diaminocyclohexane is commercially available, and is often used for the preparation of chiral salen compounds.[18] In order to avoid tedious separation of the optically active diamine, we attempted the direct use of the tartrate salt used for the resolution of one enantiomer of the diamine from the racemic mixture. Thus, the (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate was prepared according to a known procedure,[18] and 4.0 mmol of the salt were mixed with 2 equiv. of potassium carbonate in 5 ml of water, and stirred until dissolution was reached. Addition of 20 ml of ethanol caused precipitation of the salts, while heating the mixture to 60°C resulted in complete dissolution. 2 Equiv. of 2,4-di-*tert*-butylphenol and 10 equiv. of 37% aqueous formaldehyde were dissolved in 7 ml of ethanol and then added dropwise, and after heating the reaction mixture to reflux for 2.5 h, the crude product precipitated in 90% yield and was isolated by filtration (Scheme 2). The product may be further purified by flash chromatography on a silica column, using chloroform as the eluting solvent. The purified compound has a specific rotation of $[\alpha]_D^{23} = -35$ ($c = 0.6$, CH_2Cl_2).‡

This synthetic route is signified by its high convenience, as well as the wide scope of ligands that may be prepared. The starting materials are inexpensive and versatile. Furthermore, the preparation of chiral compounds is of great significance, as chiral ligands may lead to chiral complexes inducing asymmetric catalysis of various organic reactions.[17] We are currently studying the application of such chiral complexes in asymmetric catalysis as well as the application of achiral ligands in olefin polymerization catalysis and tacticity induction.[15]

† ^{1}H NMR of achiral compounds ($CDCl_3$, 200 MHz): Compound **2**: δ 7.19 (m, 12H, *Ar*OH and C_6H_5), 6.79 (d, $J = 1.9$ Hz, 2H, *Ar*OH), 3.65 (s, 4H, CH_2), 3.49 (s, 4H, CH_2), 2.67 (s, 4H, CH_2), 1.41 (s, 18H, $C(CH_3)_3$), 1.26 (s, 18H, $C(CH_3)_3$). Compound **3**: δ 7.19 (d, $J = 2.3$ Hz, 2H, *Ar*OH), 6.80 (d, $J = 2.2$ Hz, 2H, *Ar*OH), 3.70 (s, 4H, CH_2), 2.66 (s, 4H, CH_2), 2.55 (q, $J = 7.1$ Hz, 4H CH_2CH_3), 1.39 (s, 18H, $C(CH_3)_3$), 1.27 (s, 18H, $C(CH_3)_3$), 1.00 (t, $J = 7.1$ Hz, 6H, CH_2CH_3). Compound **5**: δ 6.69 (s, 2H, *Ar*OH), 6.63 (s, 2H, *Ar*OH), 3.63 (s, 4H, CH_2), 2.64 (s, 4H, CH_2), 2.27 (s, 6H, CH_3), 2.19 (s, 6H, CH_3), 2.14 (s, 6H, CH_3). Compound **6**:[13] δ 10.69 (br, 2H, O*H*), 7.22 (d, $J = 2.3$ Hz, 2H, *Ar*OH), 6.83 (d, $J = 2.2$ Hz, 2H, *Ar*OH), 3.88 (s, 4H, CH_2), 3.52 (s, 2H, N*H*), 2.99 (s, 4H, CH_2), 1.42 (s, 18H, $C(CH_3)_3$), 1.27 (s, 18H, $C(CH_3)_3$). Compound **7**: δ 7.11 (s, 2H, *Ar*OH), 6.73 (s, 2H, *Ar*OH), 3.56 (s, 4H, CH_2), 2.37 (t, $J = 7.6$ Hz, 4H, NCH_2), 2.18 (s, 6H, NCH_3), 1.69 (quin, $J = 7.6$, 2H, CH_2), 1.32 (s, 18H, $C(CH_3)_3$), 1.19 (s, 18H, $C(CH_3)_3$). Compound **8**:[13] δ 7.22 (d, $J = 2.4$ Hz, 2H, *Ar*OH), 6.86 (d, $J = 2.3$ Hz, 2H, *Ar*OH), 3.76 (s, 4H, CH_2), 3.46 (s, 2H, N*H*), 2.71 (m, 4H, CH_2), 1.76 (t, $J = 6.0$, 2H, CH_2), 1.42 (s, 18H, $C(CH_3)_3$), 1.28 (s, 18H, $C(CH_3)_3$). For compounds **1**,**4** see Ref. 15.

‡ ^{1}H NMR of (*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicyl)-1,2-cyclohexanediamine ($CDCl_3$, 200 MHz): δ 7.18 (d, $J = 2.1$, 2H, *Ar*OH), 6.79 (d, $J = 2.0$, 2H, *Ar*OH), 4.15 (d, $J = 13.6$, 2H, $ArCH_2$), 3.53 (s, 2H, N*H*), 3.46 (d, $J = 13.6$, 2H, $ArCH_2$), 2.34 (m, 2H), 2.02 (m, 2H), 1.82 (m, 3H), 1.34–1.24 (m, 3H), 1.40 (s, 18H, $C(CH_3)_3$), 1.24 (s, 18H, $C(CH_3)_3$). $[\alpha]_D^{23}$ −35 ($c = 0.6$, CH_2Cl_2).

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